Pediatric Regulations in the US and Europe

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Principles of pediatric drug development that guide regulations

- Pediatric patients should be given medicines that have been properly evaluated for their use
- Product development should include pediatric studies when pediatric use is anticipated

ICH = International Conference on Harmonization

Objectives

- Brief Overview of Pediatric History at FDA
- Review of the major elements of the US laws
- Review and comparison of the European Paediatric Regulation
- Impact for Oncology Products

US and EU Regulations

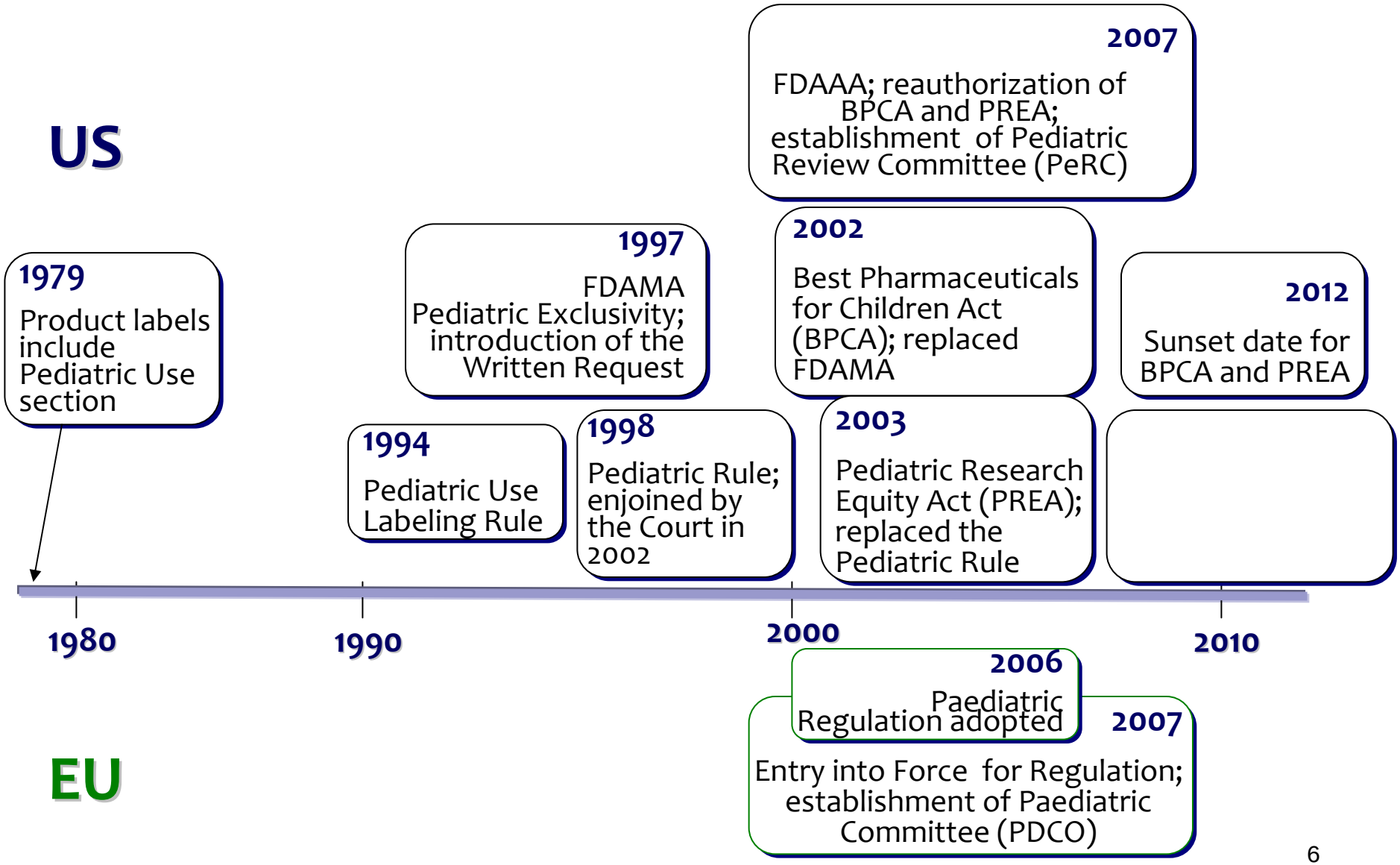
- Similar regulatory expectations
  - Study the safety and effectiveness of the drug in all appropriate age groups
  - Pediatric formulations developed
  - Labels reflect the known data
- Both regions require pediatric plans at time of submission

Acronyms

- BPCA – Best Pharmaceuticals for Children Act
- FDAAA – Food and Drug Administration Amendments Act
- PAC – Pediatric Advisory Committee
- PeRC – Pediatric Review Committee
- PREA – Pediatric Research Equity Act
- PPSR – Proposed Pediatric Study Request
- WR – Written Request

- EMA – European Medicines Agency
- PDCO – Paediatric Committee
- PIP – Paediatric Investigation Plan
- SPC – Supplementary Protection Certificate

Pediatric Regulatory History



US Pediatric Laws
PREA and BPCA: Working together


John Singer Sargent

PREA

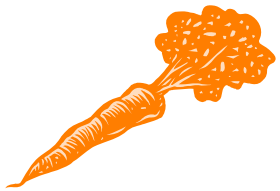
Studies mandatory

Required studies for adult indication under review

Studies for orphan indications not required

Applies to drugs and biologics

BPCA



Studies voluntary

Studies on entire active moiety

WR may be issued for orphan indications

Applies to drugs and biologics*

* Patient Protection & Affordable Care Act 2010

Pediatric Review Committee (PeRC)

- Internal Review Committee
- Membership drawn from experts across FDA including CDER, CBER, OPT
- Expertise includes

Pediatrics	Clinical Pharmacology
Chemistry	Safety
Statistics	Toxicology
Legal	Ethics

- Reviews
  - PREA - waiver and deferral requests
  - PREA - pediatric plans and pediatric assessments before approval
  - BPCA - pediatric written requests

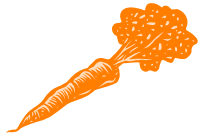
Required Studies: Application of PREA

- Pediatric studies required and a pediatric assessment must be submitted for NDA/BLA or supplements with
  - New active ingredient
  - New indication
  - New dosage form
  - New dosing regimen or
  - New route of administration
- Applies only to indication(s) included in the submission
  - Drugs with Orphan Designation to not trigger PREA
- Submission of a pediatric plan must accompany any deferral request in an NDA/BLA submission
  - Includes clinical, non-clinical and formulation plans
- PREA requirements are part of NDA/BLA approval

PREA: Waiver and Deferral

- Waiver (full or partial)
  - Study is not feasible or appropriate or safe for the age group
  - Must be supported by data
    - Use of the product in a pediatric population
    - Occurrence of the condition in the pediatric population
    - Evidence that the product would be unsafe or ineffective
- Deferral
  - Studies will be conducted later in the development of the product – usually post approval as a post marketing requirement
  - The age group(s) must be specified
  - A pediatric plan must be submitted along with the deferral request

BPCA: Written Request (WR)



- A description of pediatric studies issued by a Review Division
  - Can be in response to submission of PPSR by sponsor/applicant
  - Can be for indications and conditions other than the adult indication
- Successful completion results in an award of 6 months exclusivity attached to the patent or existing exclusivity
- PeRC review
  - What is the public health benefit?
  - Are the study designs feasible; sufficient to support dosing, safety and efficacy?
  - Have all populations and conditions been addressed?
  - Is there a PREA requirement?
  - Are there other products already approved for the condition?

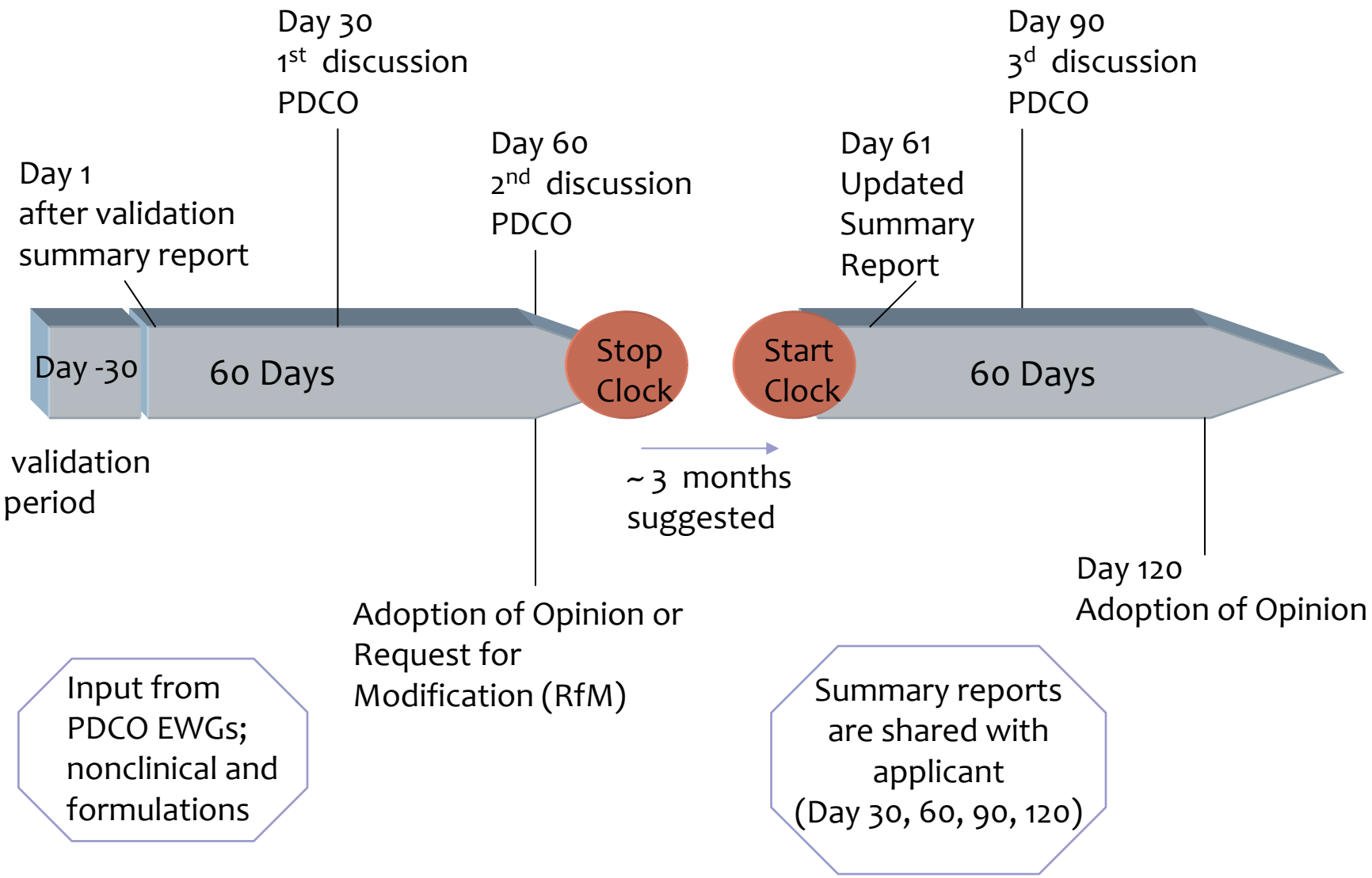
Paediatric Committee (PDCO)

- Part of the European Medicines Agency (EMA)
- Decision authority for the paediatric investigation plan (PIP)
- Composed of members with pediatric expertise from each of the 27 member states, patient/family and Health Care Professional (HCP) organizations
- Has formed Expert Working Groups (EWG) to address
  - Formulations
  - Non-clinical studies

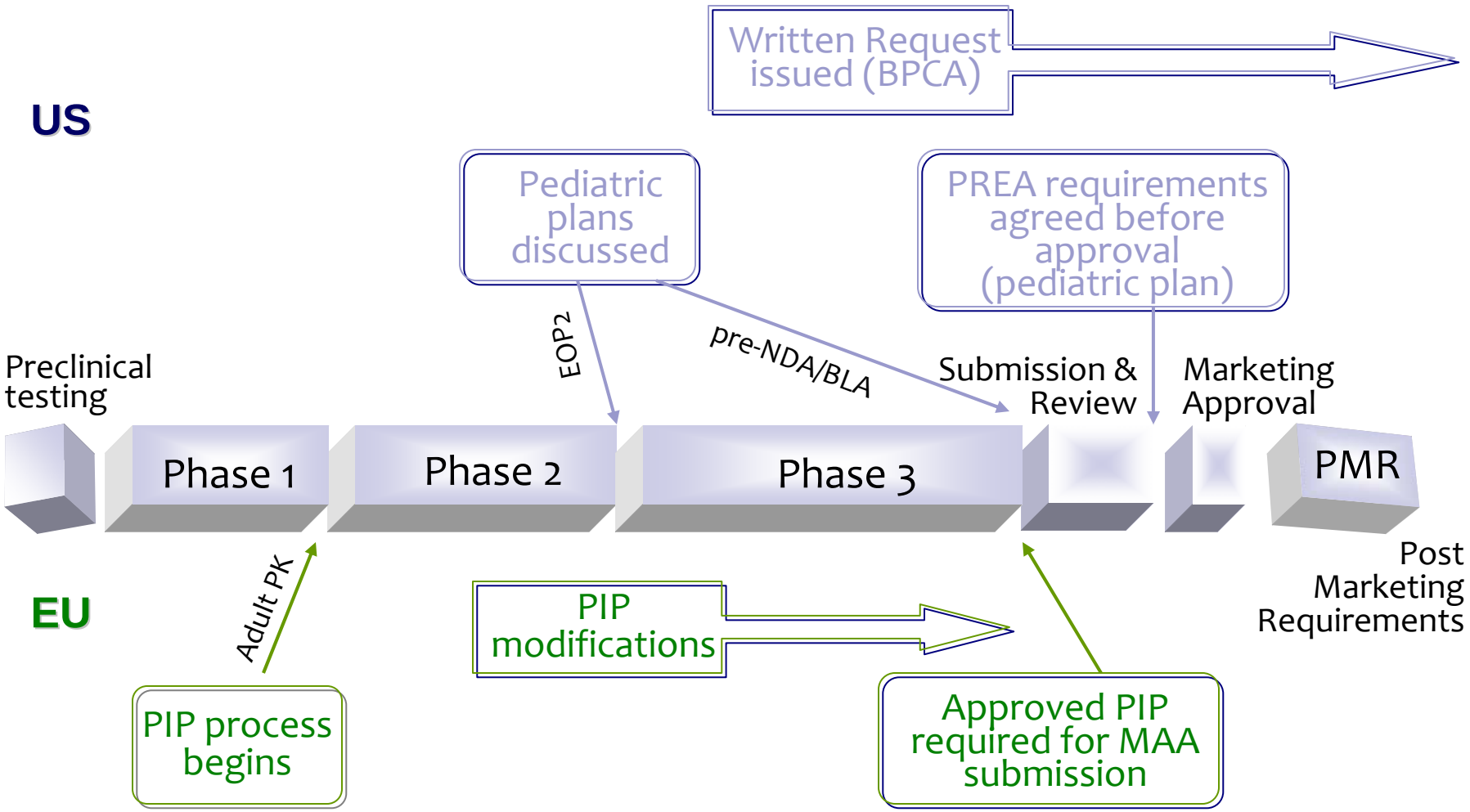
Paediatric Investigation Plan (PIP)

- One regulation that encompasses the same elements and considerations as PREA and BPCA
- An approved pediatric plan that considers all age groups, and conditions for which the product may have utility
- Opportunity for a 6 month extension of the SPC
- More structured format and timing
  - Includes waiver, deferral agreements as well as description of the studies needed; clinical, non-clinical and formulations
- Must have an approved PIP at time of filing of Marketing Authorization Application (MAA)

PIP Review Process



Pediatric Planning in the Drug Development Process - Timing



What about drugs in Oncology?

- Protocols written in conjunction with CTEP* and national cooperative research groups
- Indications likely to be studied under PREA
  - Same as adult; Leukemia/Lymphoma
  - Supportive care; to treat associated symptoms
- Majority of products will be studied under BPCA
  - Conditions under study in adults do not have a pediatric correlate
- All will follow the EU – PIP process

* Cancer Treatment Evaluation Program

Content of a Written Request

- Description of the indications to be studied
- Studies to be performed
  - Objectives
  - 1° endpoints
  - 2° endpoints
  - Statistical plans
- Nonclinical studies and formulations development – if needed
- Drug specific safety concerns
- Timing and format for report submission
- Labeling

US Pediatric Plan – Oncology product

- Phase 1 studies
  - Rationale for the starting dose
  - Pharmacokinetics
  - Definition of the maximally tolerated dose, biologically effective dose
  - Stopping rules for toxicity
  - Statistical plan
- Phase 2 studies
  - Rationale for the starting dose
  - Criteria to determine the activity of the product
  - Stopping rules based on safety or lack of activity
  - Statistical plan

US Pediatric Plan – Oncology Product

- Work done under a written request for Oncology products rarely results in a labeled pediatric indication
- Phase 3 studies are infrequent within a Written Request
  - Which disease is often at question
  - Can take many years to complete
- However, Phase 3 studies can be required as appropriate
  - Is a routine requirement for non-oncology products.

Comparing Pediatric Regulations

	US BPCA+	US PREA+	EU
Requirement	Optional Written Request	Mandatory Pediatric Plan/Assessment	Mandatory Paediatric Investigation Plan
Waiver	-	yes	yes
Deferral	-	yes	yes
Plan discussions	End of Phase 2 – post approval	End of Phase 2 – NDA/BLA approval	Completion of adult PK (Phase 1)
Plan approval	variable	with NDA/BLA approval	prior to MAA filing
Reward	Pediatric exclusivity	-	SPC* extension
Drugs	yes	yes	yes
Biologics	yes**	yes	yes
Biosimilars	yes	yes	no
Orphan drug	yes	no	yes
Decision Authority	Review Division	Review Division	Paediatric Committee

+ FDAAA 2007, * Supplementary Protection Certificate, ** Patient Protection and Affordable Care Act 2010

Summary

- Small, vulnerable populations require thoughtful, coordinated clinical trial designs
  - Global engagement with Health Authorities
- The global regulations are driving pediatric drug development
- BPCA and its incentive has been successful
  - provides a mechanism for data to be submitted to the FDA for independent review
  - expands knowledge for improved pediatric care
  - informs the product label